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MEDICAL STAFF CONFERENCE

Endocrine Manifestations of Malignant Disease

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. Sydney E. Salmon and Robert W. Schrier, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, San Francisco, Ca. 94122.

DR. SMITH:* We will devote this Medical Grand Rounds to a discussion of endocrine manifestations of cancer. Dr. Gilbert Gordan will present the case and initiate the discussion.

DR. GORDAN:† The patient for discussion today is a 50-year-old diesel engineer who presented to his private physician with complaints of nocturia and diarrhea. Initial laboratory studies revealed hypercalcemia, a low normal serum phosphate level and a high alkaline phosphatase level. He was referred to the "Bone and Stone" Clinic at the University of California Medical Center, San Francisco, for evaluation of presumed hyperparathyroidism. On physical examination he appeared chronically ill with evidence of recent weight loss. He had an enlarged right supraclavicular node, a hard tender mass in the eighth left rib and dullness at the left lung base. The liver was stony hard and descended 6 cm below the right costal margin in the mid-clavicular line.

Serum calcium was 13 mg per 100 ml, but other serum electrolytes were normal. Acid phosphatase was not increased and hematocrit and serum protein concentration were normal. The serum concentration of parathyroid hormone (PTH) as measured by radioimmunoassay was found to be increased and equivalent to that amount contained in 30 μl of a standard parathyroid adenoma extract. The combination of hypercalcemia and an elevated PTH concentration is diagnostic of hyperparathyroidism, since hypercalcemia from other causes suppresses parathyroid secretion. The hyperparathyroidism could arise from a parathyroid adenoma, from parathyroid hyperplasia or from ectopic production. The clinical evidence and the immunological studies, which Dr. Roof will discuss later, indicated that we were dealing not with a parathyroid adenoma but with hyperparathyroidism due to ectopic secretion of PTH by a nonparathyroid carcinoma. X-ray examinations were of great importance and will be discussed by Dr. Gold.

DR. GOLD:* Less than 30 percent of persons with hyperparathyroidism have roentgenographic changes in the skeleton. One such change is subperiosteal resorption. When present along the radial margin of the middle phalanges of the hands, this sign is pathognomonic of hyperparathyroidism. However, in the present case neither the hands nor the other skeletal structures manifested subperiosteal resorption. Chest roentgenogram on October 11, 1969, demonstrated recent fractures of the second and eighth left ribs, a destructive expansile lesion of the right eleventh

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rib, fluid in the left pleural cavity and a superior mediastinal mass displacing the trachea to the left. The heart, pulmonary vessels and lungs were of normal appearance. Barium enema and intravenous pyelogram studies were within normal limits. An upper gastrointestinal study revealed compression of the gastric antrum by an extrinsic mass, possibly representing enlarged lymph nodes. By January 12, 1970, radiological studies revealed multiple osteolytic lesions of the entire rib cage. The rapid progression of the osseous lesions combined with absence of subperiosteal resorption favored the diagnosis of osseous metastasis or multiple myeloma and was evidence against the diagnosis of bone disease due to primary hyperparathyroidism.

DR. GORDAN: Of most importance to us was the fact that the films of the hands showed no subperiosteal resorption. Scans of the liver and lung showed multiple defects. Bone marrow revealed only slight plasmacytosis, but no myeloma or malignant cells. Sputum cytology showed no malignant cells on multiple examinations. Histological confirmation of malignant disease was obtained by lymph node biopsy which revealed an epithelioid bronchogenic carcinoma.

Treatment with prednisone resulted in very prompt relief of pain and correction of hypercalcemia. The patient also became somewhat euphoric. Five days later, however, he had an attack of nausea and vomiting, and the serum amylase rose to 2460 International units. Acute pancreatitis may have resulted from both the hypercalcemia and the glucocorticoid hormone administration. We subsequently followed the patient in our clinic. While he was being treated with prednisone, the serum calcium level remained normal and he had no bone pain until just before he died of cerebral metastasis.

To place this type of ectopic hormone secretion in some perspective I will outline the variety of endocrine abnormalities associated with malignant diseases. Table 1 is a partial list of humoral agents extracted from tumors. The list does not include some incompletely characterized lipids, proteins and genetic materials, nor the unidentified substances presumably responsible for cutaneous and neurological manifestations of tumors. We have had some difficulty finding precise terms to describe these humoral agents. The terms "ectopic" or "inappropriate" secretion imply a knowledge of what *is* appropriate. For example, polycythemia with hypernephroma was described in 1929,[1] long before the kidney was found to produce erythropoietin normally. Webster defines "perverse" as "deviating from the norm"; and we are using that term not to be provocative or euphonious, but in the best interest of precise thought and expression.

TABLE 1.—*Pseudo-Humors from "Perverse" Tumors*

Humors	*Tumor Sites*
Parathyroid hormone-like	Lung, kidney, colon, parotid, cervix, ovary, lymphoma, liver
Calcitonin	Bronchial carcinoid
Anti-Vitamin D	Bone and blood vessel
ACTH and MSH-like; CRF	Lung, thymus, pancreas
Antidiuretic hormone	Lung, pancreas, prostate
Erythropoietin	Cerebellum
Insulin-like	Liver, adrenal cortex, large fibromas or sarcomas
Chorionic gonadotrophin	Liver, adrenal cortex, lung, esophagus
Growth hormone	Lung, endometrium
Placental alkaline phosphatase	Lung, breast, colon, ovary, pancreas, stomach, cervix, lymphoma
Thyrotrophin-like	Choriocarcinomas, moles, testis
Phytosteryl esters	Breast, thyroid, uterus, ovary, kidney

The clinical findings associated with these perverse humoral secretions may be incomplete or entirely lacking. Adrenocorticotrophin-hormone (ACTH)-secreting tumors were first recognized in patients with lung cancers or thymomas because of the clinical manifestations of Cushing's syndrome. W. Hurst Brown,[2] a chemical pathologist at St. Mary's Hospital in London, actually described such a case in 1928, four years before Harvey Cushing's classic description of the syndrome. It was subsequently recognized that the syndrome associated with tumors was often clinically incomplete, manifested only by hypokalemia and diabetes mellitus.[3] Still later, it was found that blood corticoid levels are often increased in patients who have bronchial carcinomas, adenomas or carcinoids and are without clinical manifestations.[4] It is now known that ACTH and melanocyte-stimulating-hormone (MSH)-like peptides are found in the blood of many patients with tumors but with no clinical or chemical evidence of hypercorticism.[5] Similarly,

just a quarter of a century after Albright[6] had postulated secretion of a PTH-like substance from a kidney tumor to explain the associated hypercalcemia and hypophosphatemia, Berson and Yalow[7] showed that many patients with lung cancer have immunological PTH-like material in their blood in the absence of hypercalcemia.

As a corollary, screening of the blood of suspected cancer patients for tumor peptides by radioimmunoassay may allow earlier detection and thus lead to better treatment of tumors. For example, cancers of the lung, pancreas, colon, and kidney are often discovered at an untreatable stage; these tumors are known to produce measurable peptides. Peptides might also signal early recurrence, such as in choriocarcinomas which are monitored by blood and urine chorionic gonadotrophin levels. Thus, monitoring of cancers may greatly improve therapy as demonstrated in the treatment of choriocarcinomas of women which are now often curable even when disseminated.[8] Certain humors are specific for certain tumors.[9] Some tumors, such as bronchogenic carcinoma, are very versatile and may harbor multiple, measurable peptides,[10] as well as other, at present undefined, compounds. In contrast, PTH-like substances are seldom if ever made by human breast cancers; therefore, there has been no difficulty diagnosing coincidental parathyroid adenomas in patients with breast cancer.[11,12,13]

In addition to PTH, certain tumors make other substances which affect calcium metabolism. Milhaud[14] has found calcitonin by bioassay of bronchial carcinoids. Of particular interest are the half dozen cases of vitamin D-resistant osteomalacia or rickets due to an unknown substance from benign hemangiomas or bone tumors.[15] After removal of the tumor, vitamin D resistance disappeared, and the bone lesions healed. Cushing's phenomena, clinical or chemical, may arise not only from ectopic elaboration of ACTH- and MSH-like peptides but also, as Upton and Amatruda[16] have recently shown, from corticotrophin-releasing factor.

The syndrome of inappropriate secretion of antidiuretic hormone has been associated with many tumors, notably those of the bronchus, pancreas and prostate. In some cases vasopressin-like material has been extracted from the serum, tumor and metastatic lesions.[17] Polycythemia occurs "appropriately" with certain kidney tumors and even cysts. A tumor-elaborated erythropoietic substance producing polycythemia in patients with cerebellar hemangioblastomas seems, in our present state of ignorance, "inappropriate," "ectopic," or "perverse." There is another form of polycythemia, however, seen with uterine fibroids and sarcomas where erythropoietic activity has not yet been demonstrable.

Hypoglycemia occurs most commonly with very large retroperitoneal fibromas or sarcomas, hepatomas, or cancers of the adrenal cortex. In almost all of these tumors insulin is not to be found, but in many the rat epididymal fat pad assay recognizes an insulin-like material. Chorionic gonadotrophin from tumors of the adrenal cortex or liver produces precocious puberty in boys or gynecomastia in adult males. Rosen[18] also demonstrated chorionic gonadotrophin in bronchogenic carcinoma with gynecomastia. Although growth hormone has been found in bronchogenic carcinoma, it is not clear whether it produces any clinical manifestations. The suggestion that it might be responsible for clubbing has not been substantiated.[19] Similarly, the placental alkaline phosphatase, or Regan isoenzyme, which Fishman et al[20,21] have so carefully studied in many human cancers and in Hela cells does not at present appear to produce any clinical manifestations. Thyrotrophic activity in hydatidiform moles and choriocarcinomas was first described by Tisné[22] in 1955. It is usually associated with an increase in protein-bound iodine and thyroxine levels and radioiodine uptake without clinical hyperthyroidism. Rarely, the complete clinical syndrome of hyperthyroidism has been reported with these tumors or with embryonal carcinoma of the testis.[23]

Finally, nonpeptide compounds have also been found. We first extracted phytosterols and phytosteryl esters from breast cancers.[24] These compounds, particularly the short-chain esters, have potent calcium-mobilizing activity (some more powerful than vitamin D or even 25-hydroxycholecalciferol). Robert Brown et al[25] and others have confirmed the presence of these sterols in breast cancers, and Day et al[26] have extended the finding to other tumors. The possibility of these agents contributing to the hypercalcemia of breast cancer is under active investigation in our laboratory.

To summarize, many humoral agents have been implicated in syndromes caused by tumors,

TABLE 2.—*Comparisons of Hormone-like Activities Secreted by Tumors to Normal Hormones*

Hormone Activity:	TSH-*like*	ACTH-*like*	MSH-*like*	PTH-*like*
Molecular weight	Greater than pituitary TSH	Unknown. More large molecules than pituitary ACTH	Different from pituitary MSH	Similar to PTH
Bioassay activity	Positive; longer acting than pituitary TSH or LATS	Decreased in relation to immunoassay	Increased in relation to immunoassay	Not accomplished
Immunological characteristics	Differs from pituitary and placental TSH	Similar to pituitary ACTH	Similar to pituitary MSH	Differs from authentic PTH
Amino acid composition or sequence	Unknown	Different from pituitary ACTH	Unknown	Unknown

both benign and malignant. In many cases, metabolic complications result which can be of clinical importance for the patient and, in some cases, may be the first evidence of tumor. Not all tumors make all humors, a point of some diagnostic importance. It may be hoped that this phenomenon will be exploited for the early detection and better treatment of patients with cancer.

Dr. Roof will now describe recent results obtained with radioimmunoassay techniques.

DR. ROOF:* Many tumors produce hormones apparently perverse for them. Originally, development of characteristic clinical syndromes alerted the physicians to their presence. More recently, as more sophisticated and sensitive assay techniques have been perfected, a wider variety of ectopic hormones have been demonstrated in the serum, as well as in tumors of a larger number of patients. Final proof of production of the ectopic hormone by tumor has usually rested upon extraction of the tissue and demonstration that the extracted material gives the typical required effects by bioassay, chemical methods or immunoassay. Similar syndromes can arise from multiple mechanisms. For example, hypoglycemia might be produced by insulin, or by excessive consumption of sugar by large non-pancreatic tumors without immunologically identifiable insulin, or by other insulin-like substances. Stimulation of thyroid activity can be produced by thyrotrophin of pituitary origin, placental origin, or by long-acting thyroid stimulators or still other thus far unidentified substances. In extracts of the tumors producing PTH-like and ACTH-like hormones the concentration of the ectopic hormone has been quantitatively minute. Quantitations of 1 to 10 μg per gram of dried tissue[27] (or one-thousandth to one-thirtieth of that seen in the gland which normally produces it) have been made of the concentration of the PTH-like hormone in tumors. The enormous size of the tumor compared with the normal hormone-producing tissue thus may provide amounts of ectopic hormone sufficient to produce the clinical picture. With most ectopically produced hormones, the amount of material available has so far been insufficient for determination of amino acid sequence.

Some comparisons of hormone-like activities secreted by tumors to normal hormones are shown in Table 2. At least two of the ectopic hormones, TSH-like and ACTH-like, are more effective than their normal counterparts. The TSH-like hormone found in hydatidiform moles has been shown to have a more prolonged duration of action than that of pituitary TSH, yet is not the long-acting thyroid stimulator (LATS) of Graves' disease.[28]

Ectopically produced ACTH-like activity is frequently in great excess of normal concentrations. In such instances cortisol output by the adrenal glands may be increased threefold, and urinary 17-ketosteroids may be increased fivefold.[29] Nonetheless, on bioassay the activity of the ACTH-like peptide is less than would be expected from the immunoassay.[30] However, it is similar to pituitary ACTH chromatographically[31] with parallel

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dose response curves in steroid production and ascorbic acid depletion assays, as well as having similar enzymatic and chemical inactivation.[32] It also has immunological cross reactivity with normal ACTH, as demonstrated with immunofluorescence and immunoassay.[33] Recently Amatruda[30] reported that the amino acid content of the tumor ACTH-like peptide differs from that of pituitary ACTH. Yalow and Berson[34] described heterogeneity as a normal characteristic of all glandular and plasma peptides for which they have immunoassays. In the case of ACTH, two component families of molecules which differed greatly in size were demonstrated. They postulated that the larger molecule may be bound covalently to a larger peptide because the much larger molecule traversed the Sephadex column with albumin. The usual ACTH sized molecule was found in tissue extracts but not in the plasma of a patient with ectopic Cushing's syndrome due to association with thymoma.[34] The larger ACTH-like peptide could be demonstrated in the plasma. Thus, the apparent abnormality of the ectopic hormone might reflect a quantitative alteration in the concentrations of normal components. The greater apparent activity of these ectopic hormones may be because of lack of the normal feedback (as by dexamethasone in the case of the ACTH-like hormone[35]) or because of loss of normal degradation, in that abnormal sequences may not be as susceptible to normal catabolic mechanisms.

MSH has been found in all tumors where ectopically produced ACTH has been found.[36] By radioimmunoassay, both α and β ectopic ACTH react the same as those of pituitary origin.[37,38] In three tumors Liddle et al[27] found more biological MSH activity present than could be accounted for by their content of immunoreactive α or β MSH and ACTH, and it could be separated from these substances by column chromatography. Ectopically produced antidiuretic-hormone (ADH), erythropoietin and calcitonin have yet to be studied in this fashion. The amino acid content of two ectopically produced corticotrophin-releasing factors (CRF) has been determined.[16] However, the amino acid content and sequence of normal CRF is not known at present.

In 1941 Fuller Albright[6] used the term "parathyroid hormone-like substance" to explain the hypercalcemia and hypophosphatemia accompanying a carcinoma of the kidney. Collip's[6] bioassay of that tumor was negative. In fact, to date no parathyroid-like material has been active by bioassay. Sherwood[27] noted that the concentration of the PTH-like material produced in the tumors is so small that current methods of bioassay are not sensitive enough to detect them unless extremely large amounts of tumor efficiently can be extracted and concentrated to a small volume. Since then, the laboratories of Tashjian and Munson[39] and Sherwood et al[27] have used immunological techniques to show PTH-like material in a variety of tumors originating in colon, ovary, lung and parotid gland. With the development of the radioimmunoassay for PTH, Berson and Yalow[7] have shown elevated plasma levels of PTH in 7 of 27 normocalcemic patients with lung cancer. Sherwood et al[27] examined tumor extracts with their radioimmunoassay and showed the PTH-like material to be similar to normal PTH using a single antiserum.

We have examined sera from 50 patients with cancer of tissues other than the parathyroid and the breast, using a radioimmunoassay for parathyroid hormone. Of these, 25 patients had hypercalcemia and hypophosphatemia; the remainder were normocalcemic or even slightly hypocalcemic. None of the patients had uremia, a condition known to cause increased serum PTH levels. In addition, five tumors associated with hypercalcemia and hypophosphatemia were extracted and examined by radioimmunoassay. Using antiserum developed in a guinea pig to beef PTH, we found significant PTH levels in the face of hypercalcemia in 60 patients with proved parathyroid adenomas.[40] This specific assay was also used to test sera from patients with cancer (Chart 1). Values on the patient discussed today are indicated in Chart 1. Both the hypercalcemia and serum PTH levels decreased on prednisone therapy, suggesting that corticoids may have alleviated hypercalcemia by inhibiting ectopic hormone secretion. In confirmation of the results of Berson and Yalow[7] we found that some normocalcemic patients with adenocarcinomas or oat cell carcinomas of the lung had high levels of PTH. Although other explanations are possible, the lack of hypercalcemia suggests that this ectopic PTH is biologically inactive.

We also used two antisera to bovine PTH which were developed in guinea pigs and chickens with equal sensitivity to human PTH (Chart

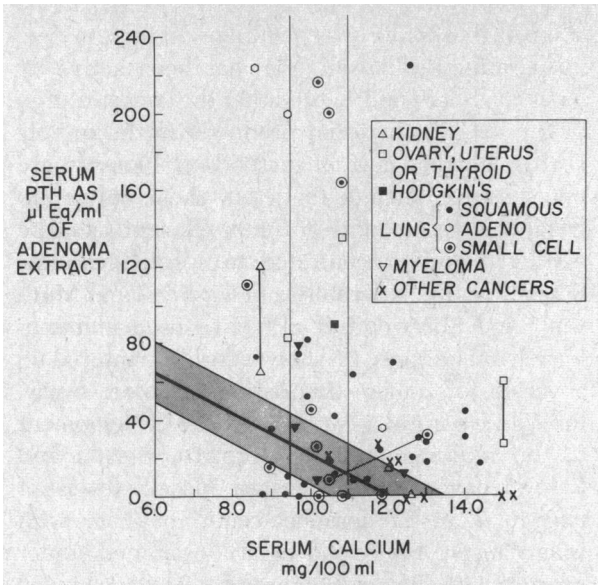

Chart 1.—Serum PTH and calcium concentrations in patients with cancer (excluding breast cancer). The patient discussed is represented by the two dots connected by a line.

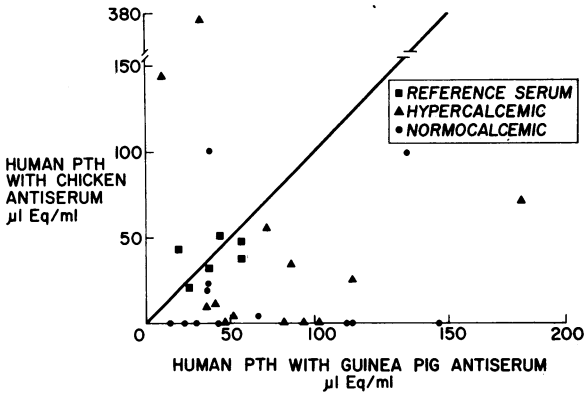

Chart 2.—Comparative measurements of serum concentrations of human PTH with two different antisera (chicken and guinea pig). Cancer patients (excluding breast cancer) had different values for serum PTH with the two antisera. (See text.)

2). With these two antisera, we have examined 26 serum specimens from patients with malignant lesions other than breast cancer. In 12 serum samples the chicken antiserum failed to recognize any immunoreactive PTH. In all but three specimens tested, the guinea pig antiserum gave higher values than did the chicken antiserum. In these three, the chicken antiserum recognized an immunoreactive PTH at three to ten times the level detected by the guinea pig antiserum. We believe that the chicken antiserum and guinea pig antiserum are reacting with different portions of the PTH-like molecule.

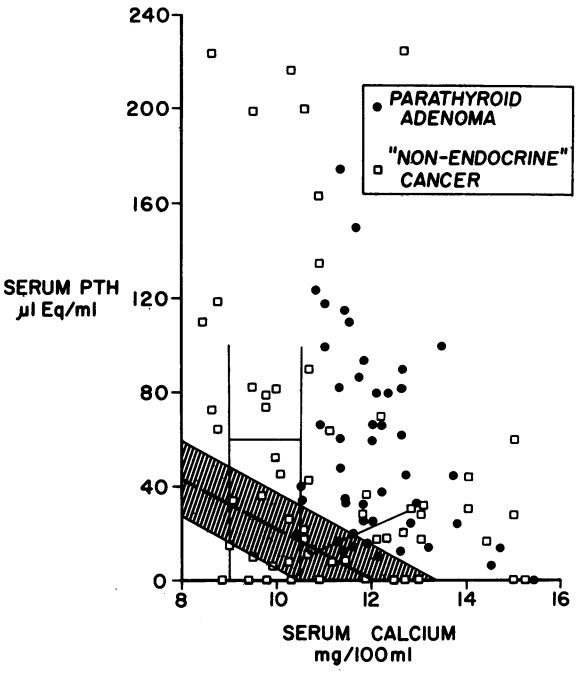

Chart 3.—Comparison of serum PTH and calcium concentrations for patients with parathyroid adenomas and patients with non-endocrine cancers. A decided overlap was observed in these two groups.

The minimal number of amino acids necessary for antigenicity is not known; however, in the case of sugars, three to five may be the minimal number.[41] The fact that the two anti-sera detect different amounts of immunoreactive PTH in the sera could possibly be due to differences in amino acid sequence in the ectopic PTH and normal PTH.

Riggs and Arnaud[42] recently confirmed and extended our claim of immunological abnormality of ectopic PTH. They also used two antisera, one developed in the guinea pig to porcine PTH and one in the chicken to porcine PTH, to evaluate 18 patients with ectopic hyperparathyroidism due to nonparathyroid cancer without apparent skeletal metastasis. Immunoreactive PTH was found to be lower in the cancer patients than in patients with adenomas of the parathyroid and similar degrees of hypercalcemia. Thus, the immunoassay could differentiate ectopic hyperparathyroidism from parathyroid adenoma as the cause of hypercalcemia in 16 of the patients. This differs from our experience which is summarized in Chart 3.

As shown in Table 3, the serum concentrations of PTH found in our patients with parathyroid adenomas and in those with overt malignant dis-

TABLE 3.—*Serum Calcium Concentrations and* PTH *Levels Associated with Parathyroid Adenomas and Non-parathyroid Malignancies*

No. of patients	*Group*	*Serum Ca mEq/L±SE*	PTH *μeq/ml*
60	Normal	5.0 ± .03	20 ± 2
59	Parathyroid adenomas	6.1 ± .05	57 ± 4
NON-PARATHYROID CANCERS			
26	Normocalcemic	4.8 ± .04	55 ± 7
24	Hypercalcemic, hypophosphatemic	6.3 ± .09	32 ± 5
94	Breast Cancers	4.9 ± .02	20 ± 1

ease overlapped for any level of serum calcium concentration. The mean serum calcium of cancer patients with hypercalcemia and hypophosphatemia was slightly higher than in the patients with parathyroid adenomas; however, the mean PTH level was lower than in the patients with adenomas. Interestingly, the women with metastatic breast cancer had normal calcium and PTH concentrations. This indicates that breast cancers do not make parathyroid hormone. How the PTH from cancers differs from PTH of normal, adenomatous or hyperplastic parathyroid glands is unknown. Berson and Yalow[43] have shown that peptides may occur in at least two families of molecules. By using two antisera, two immunoreactive PTH's were found with different disappearance rates after parathyroidectomy. Arnaud et al[44] and Sherwood et al[45] also postulated heterogeneity for PTH in which the molecule found in the gland is larger than the secreted hormone. Thus, a variety of PTH molecules may occur normally which differ in size, and the ratio of these different sized molecules may be altered in cancers.

In extracts of five tumors associated with hypercalcemia and hypophosphatemia, we found some reactivity in the radioimmunoassay. Using these extracts thus far, we have failed to obtain curves of dilution which can be superimposed totally on those of highly purified beef PTH standard, or partially purified, human parathyroid hormone. However, estimation of PTH-like immunological activity present in our extracts agreed well with the ranges found by Sherwood et al[27] in the seven tumors where PTH-like activity was present. Unless it can be shown that the apparent abnormality of ectopic PTH relates to an altered amino acid sequence, an abnormality secondary to a genetic failure or other mechanisms is not yet warranted.

In summary as numerous hormones produced ectopically have been studied by a greater variety of tests, what was thought initially to be identical with the native, or naturally produced hormone, has increasingly been shown to be nonidentical. In none do we know the amino acid sequence and in only one (ectopic ACTH) is abnormal amino acid content claimed. At present more than 14 humors have been described as tumor-produced. Of these, five which have been carefully studied (PTH-like, ACTH-like, MSH-like, TSH-like and placental alkaline phosphatase from bronchogenic carcinoma) have been shown to be dissimilar to the familiar peptide. ADH and erythropoietin by existing tests have not yet been shown to be different from the normal hormone. Ectopically produced anti-vitamin D and calcitonin have not yet been studied in detail. Although the amino acid content of two ectopic CRF's has been determined, the content and sequence of normally occurring CRF at present is not known.

DR. SMITH: Dr. Gordon Tomkins will discuss possible molecular mechanisms of ectopic hormone formation.

DR. TOMKINS:* In considering this subject, decision must be made as to whether the hormonally active substances produced by certain malignant cells are normal products of those cells or represent some alteration in gene expression. Since the process of malignancy causes cells to divide in an uncontrolled way, it is capable of "amplifying" the population of any given cell on the body. Thus, if a cell which is present in small numbers in the body normally produces a hormonal substance and subsequently becomes malignant, the descendants of these cells could produce "ectopic hormones" even though the active product is perfectly normal for that particular cell.

On the other hand, it may be that cells which normally never produce hormones do so when they become malignant. Possible reasons for this aberration are legion. For instance, most cells which are not normally dividing are usually blocked in the period of cell division cycle following mitosis but previous to DNA synthesis. However, there are certain cellular products

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which are known to be produced only at other times in the cycle. It is conceivable, therefore, that when cells become cancerous and enter into the division cycle, parts of the genome which are normally inactive become functional as a consequence of cell division.

The basic cellular lesion which results in malignant change is not yet understood, and for the moment it is possible to entertain the idea that this aberration may somehow interfere with the normal controls over gene expression. These controls are understood, at least in microorganisms, in reasonable detail; and from our knowledge of them it is apparent that gene expression (that is, messenger ribonucleic acid (RNA) synthesis) requires that RNA polymerase attach to a particular sequence of bases in the deoxyribonucleic acid (DNA) which denote "start transcription here." In addition, the attachment of the RNA polymerase to certain genes often requires the presence of additional protein factors and small effector molecules such as cyclic adenosine monophosphate (AMP).

When the polymerase is correctly attached, transcription may not yet take place because the gene in question might be under "negative" control. That is, there may be another gene-specific protein molecule (a repressor) which blocks the action of the polymerase. If this is the case, the repressor must be detached from the DNA by interaction with a specific effector molecule called an "inducer." Once the polymerase has been allowed to begin transcribing a particular gene, regulation of this process continues since there are likewise "end transcription here" signals in the DNA as well; and these may either allow termination or be disregarded, depending on the presence or absence of additional regulatory molecules.

In mammalian cells when the initiation, elongation and termination of messenger RNA molecules has taken place, it must be further "processed" in order to become a functional template for protein synthesis. This is a complicated and largely mysterious reaction involving the removal of extraneous nucleotides and sometimes the addition of other nucleic acid elements such as polyadenylic acid. Only processed messenger appears to be transported from the nucleus to the cytoplasm where its information is translated into polypeptide sequences.

There also appears to be specific regulation as to the initiation of the translational process. Finally, the polypeptide resulting from the translation may not be biologically active directly but must sometimes undergo "post-translational modification," a reaction in which certain amino acid residues are removed, allowing the protein to undergo changes in conformation which are required for its ultimate biological activity. In addition, many proteins are rapidly degraded intracellularly by apparently specific mechanisms. Obviously, abnormalities in any step of this complicated sequence of events could lead to anomolous gene expression—that is, to the appearance of gene products not normally manufactured by a particular cell.

Additional theoretical explanations for ectopic hormone production might be suggested on the basis of the probable viral cause of malignant disease. It might be that tumor viruses carry extraneous genetic material which is added to the normal genetic complement of the cell. In this way, although it seems rather unlikely, the expression of the exogenous genetic information could result directly in anamalous protein production.

However, it should be clear, even from this brief discussion, that before any molecular mechanism can be given serious consideration, a great deal more information must be obtained about both the ectopic hormones themselves (in particular their amino acid sequence) and the genetic regulation in human cells. Until this basic knowledge is available, speculations about the cause of anomalous protein production, although interesting, are not likely to be near the mark.

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GAMMA GLOBULIN—PROTECTION AGAINST VIRAL HEPATITIS?

Recently at the Los Angeles County General Hospital we studied a series of nurses and physicians who were accidentally stuck with needles used on patients with known viral hepatitis. In 12 such instances the patient with hepatitis was Australia antigen-positive. Five of the personnel undergoing this accidental exposure developed frank hepatitis. All 12 of the individuals having this contact received 30 ml of gamma globulin in an attempt at prophylaxis—post-exposure prophylaxis. The attack rate of 40 percent is just too high for anyone to believe that the globulin was providing any protective effect at all. In fact, one can state fairly safely that there is no evidence at all that globulin provides any protection for antigen-positive hepatitis either from person-to-person contact or parenteral forms of contact.

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